

REVIEWS

Cetuximab for head and neck cancer: From bench to clinic

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Abstract

Background: Molecular targeting drugs (MTG) have proved effective for head and neck cancer (HNC) not only in basic studies but in many clinical trials. Cetuximab, an anti-EGFR monoclonal antibody, is a key drug for regimens including MTG. Cetuximab binding to the EGFR blocks phosphorylation and activation of receptor-associated kinases and their associated downstream signalling (MAPK, PI3Kinase/Akt, STAT3 pathways) resulting in inhibition of cell survival and proliferation. Cetuximab with chemotherapy or radiotherapy is reported to be effective in preclinical studies, and combining cetuximab with chemotherapy or radiation therapy extends survival in head and neck cancer in clinical studies. However, monotherapy with cetuximab has shown limited success, although monotherapy with cetuximab is effective in preclinical studies. We focus on the fact that the evaluation of the mono administration of cetuximab in preclinical studies does not match that in clinical studies, even though the efficacy of the coadministration of cetuximab with chemotherapy or radiotherapy in preclinical studies almost matched those in clinical studies. Molecular crosstalk has been observed between EGFR and IGF1R signaling through the PI3kinase/Akt pathway, as has molecular crosstalk between the EGFR and gp130 signaling pathways through STAT3 pathway. Therefore, the combination of cetuximab with an agent that inhibits the activation of both Akt and STAT3 may overcome resistance to cetuximab in HNC. We performed a review of the literature to investigate this possibility.

Methodology: A review of the literature from 1993-2012.

Conclusions: Coadministration of cetuximab and drugs which inhibit Akt and STAT3 may significantly increase the monoadministration response rate of cetuximab. Trials suggest that the addition of drugs which inhibit Akt and STAT3 may increase efficacy to that above currently-observed synergistic effects of the coadministration of cetuximab with existing chemotherapy or radiotherapy.

Key words

Cetuximab, Head and neck cancer, Resistance, Crosstalk

1 Introduction

Approximately 90% of head and neck cancers are squamous epithelial cell epithelial cancers. Currently, 70-80% of those are advanced cancers with poor prognosis, and therefore some researchers emphasize the importance of multidisciplinary treatment. For cases with advanced cancer for which radical surgery can be performed, the standard therapy is either

post-operative radiation with radical surgery and chemotherapy, or concurrent chemoradiation therapy (CCRT). CCRT is the simultaneous treatment with chemotherapy using drugs with high anti-tumor efficacy, such as cisplatin (CDDP), and radiotherapy at a curable dosage, with the aim of functional preservation.

Multidrug concomitant therapies and CCRT are proactively performed on advanced head and neck cancers. Such therapies have been highly efficacious in shrinking cancers. However, notwithstanding various multidisciplinary treatments, there has not been sufficient improvement in the prolongation of survival time and the reduction of distant metastases in advanced head and neck cancers. Meanwhile, various molecular-targeting drugs have been developed in recent years and there are also reports on noteworthy results in breast cancer, colon cancer, malignant lymphoma, and chronic myelogenous leukemia. There have not been any molecular-targeting drugs which have been approved with an indication for head and neck cancer by the Ministry of Health, Labour and Welfare in Japan. However, there has been progress in a large number of clinical trials on molecular-targeting drugs in the US and Europe. Molecular-targeting drugs have been concomitantly administered with anti-cancer agents and radiotherapy. In particular, the receptor of epidermal growth factor (EGFR), which is involved in tumor growth, is found in head and neck squamous epithelial cell cancers at high frequency. There has been progress in various basic and clinical studies on major molecular-targeted drugs which inhibit this receptor in head and neck cancer. There are two types of EGFR inhibitors, namely EGFR tyrosine-kinase inhibitors such as gefitinib, erlotinib and lapatinib, as well as cetuximab, which were developed as anti-EGFR monoclonal antibody. This paper reports on basic and clinical studies in which cetuximab is used for head and neck cancer due to the following reasons in Japan: EGFR gene mutations related to EGFR tyrosine kinase high sensitivity in clinical samples of head and neck cancer patients are extremely rare ^[1]; and meta-analyses in clinical studies in the US and the Europe have found that cetuximab is more efficacious for head and neck cancer than EGFR tyrosine kinase inhibitors ^[2].

2 Pre-clinical studies using cetuximab

2.1 Mono administration evaluation

1) *In vitro* and transplantation *in vivo* studies have shown that the processing and administration of cetuximab inhibit the proliferation of human tumor cells derived from various organs, such as head and neck squamous epithelial cell cancer, pancreatic cancer, colon cancer, renal cancer, prostate cancer and bladder cancer, in which EGFR is found and which depend on EGF and TGF α ^[3,4]. It is believed that the cell cycle mechanism is controlled at the G1 stage, and the number of cells at the S stage is observed to decrease. It is believed that the decrease in cells at the S stage is due to cetuximab promoting the expression of p27^{KIP1}, and inhibiting cyclin-E and CDK2 activities, leading to the inhibiting of cancer cells ^[5-7]. Moreover, Bcl2 expression is inhibited through cetuximab processing, and promotes expression Bax and caspase 3, 8, and 9, leading to apoptosis, and this has an anti-cancer action ^[8-10]. There are reports on the anti-angiogenic effect of cetuximab due to the inhibition of angiogenesis factors such as in IL-8, bFGF, and VEGF. In particular it is believed that the inhibition of VEGF production in cultured supernatant, and in clinical studies with cetuximab processing, is one of the anti-tumor mechanisms of cetuximab ^[11-13]. Additionally, it is also observed that stimulation with EGF accelerates the expression of MMP9, which is a metastasis factor; and the administration of cetuximab is also observed to decrease MMP-9 expression in cancer cells and to inhibit metastasis ^[14].

2) Cetuximab leads to the internalization of EGFR. It is suggested that this leads to down-regulation of receptors ^[15]. Therefore the down-regulation of cell-surface EGFR due to cetuximab may influence the inhibition of receptor signals.

3) Depending on the site of Fc (antibody crystal fragments), cetuximab leads cytotoxic immunity effector cells towards EGFR-expressing cancer cells. Therefore cetuximab induces antibody-dependent cellular cytotoxicity (ADCC) orientated towards tumors ^[16].

2.2 Concomitant administration of cetuximab chemotherapy and radiotherapy

Although different drugs were investigated by organ and tissue type, additive and synergistic anti-cancer effects have been demonstrated with concomitant treatment using cetuximab and chemotherapy. The efficacy of concomitant therapy of doxorubicin and cetuximab has been observed in squamous epithelial cell cancer and in breast cancer^[17]. The efficacy of concomitant therapy of cetuximab and CDDP is observed in oral squamous epithelial cell cancer^[18]. The effect of concomitant administration of cetuximab and topotecan is observed in colon cancer, ovarian cancer and breast cancer^[19]. The co-administration of cetuximab and paclitaxel cells is observed to be efficacious in bladder cancer^[14]. Additionally, the effect of the concomitant therapy of cetuximab and gemcitabine is observed in pancreatic cancer^[20]. It is believed that cetuximab has co-administrative effects such as inhibiting the abovementioned angiogenic factors and inhibiting restoration of DNA dysfunction induced by chemotherapy. In addition, concomitant therapy with radiotherapy has been investigated. It is believed that the mechanism of concomitant therapy with radiotherapy is that the administration of cetuximab decreases the number of cells in the S stage, increases that in the G1 stage, in which cells have a high radiotherapy sensitivity compared to in the S stage in which they are radiotherapy resistant; and reduces glutathione which is a free radical scavenger with an impact on anti-cancer efficacy of radiotherapy^[9, 13].

Further, there are reports on concomitant therapy of cetuximab with radiotherapy inhibiting STAT3 expression, which inhibits apoptosis, leading to the promotion of apoptosis and increasing anti-cancer efficacy^[21].

3 Clinical studies using cetuximab

3.1 Monotherapy with cetuximab

Monotherapy evaluation is mainly carried out on cases which are resistant to platinum agents such as CDDP. Its response rate is approximately 10%^[22].

3.2 Concomitant therapy of cetuximab chemotherapy and radiotherapy

The key drug in chemotherapy for head or neck cancer is CDDP, and various anti-cancer agents are combined mainly with CDDP for chemotherapy. Additionally, the efficacy of the concomitant therapy of CDDP and cetuximab has been investigated in various phase II clinical studies^[23]. Based on the results of such studies, Burtness conducted and reported on a large phase III study in which the efficacy of concomitant therapy of CDDP and cetuximab was compared and investigated in cases of metastatic relapsed head and neck cancer in the Eastern Cooperative Oncology Group (ECOG)^[24]. This was a double-blind study in which cases with relapsed metastatic squamous epithelial cell cancers with lesions which could be evaluated were randomly allocated to the CDDP plus cetuximab group (Arm A) or the CDDP plus placebo group (Arm B). In the study, cetuximab concomitant therapy was provided to cases who were PD in Arm B. Fifty-seven cases were registered in Arm A and sixty in Arm B, and 65% of subjects were cases with distant metastases. The response rate in Arm A was 26.3% and that in Arm B was 9.8%. This showed that the response rate was significantly higher in the cetuximab concomitant arm; however the median survival periods were 4.2 months and 2.7 months for Arms A and B, respectively. The median non-exacerbation survival periods were 4.2 months and 3.1 months, respectively. There were no significant differences in the above two median values. The skin toxicity in the cetuximab concomitant therapy group was significantly deteriorated, and a significant prolongation of the survival period was reported in cases in which skin toxicity was observed. The most important clinical study on relapsed and metastatic cancer was the Extreme Study carried out by Vermoken *et al.*^[25]. This study had two groups, Groups A and B. Group A was administered cetuximab in addition to concomitant therapy of 5-Fu with CDDP or carboplatin; and Group B was not administered cetuximab, but was co-administered 5-FU and CDDP or carboplatin. This was a large comparative study in which 420 cases from 17 European countries were registered. After 6 courses of chemotherapy were provided and cetuximab administration was further

continued in Group A, treatment was continued to be provided until the cancer grew or until side effects occurred which made it impossible to continue the therapy. Side effects included skin rash and allergic reaction due to the concomitant administration of cetuximab. However there were no differences in other side effects such as myelotoxicity between the two groups. In addition, the average survival periods in both groups were significantly prolonged. The average survival period in the cetuximab concomitant therapy group was 10.1 months and that in the non-concomitant group was 7.4 months. This was a noteworthy report which demonstrated prolongation of the survival period in treatment for relapsed metastatic cancer.

Ang *et al.* performed a phase III study with the Radiation Oncology Group (RTOG) on locally advanced head and neck cancers. They reported that EGFR expression is a factor of poor prognosis which is independent of local control in radiotherapy and the survival period^[26]. Additionally Robert *et al.* set the dosage of cetuximab administered with radiotherapy^[27]. According to the, the recommended dosage of cetuximab is 400 g/m² one week prior to exposure and 250 mg/m² weekly during exposure. Further, Bonner *et al.* reported on a phase III study on cetuximab combined with radiotherapy^[28]. According to their report, there was no exacerbation of side effects due to the co-administration of cetuximab, and the 50% survival time was extended from 29 to 49 months relative to the group to which only radiotherapy was provided. The 3-year overall survival rate in the cetuximab-administration group improved from 45 to 55%, and the three-year local control rate was significantly improved. Pfister *et al.* reported on a phase II study in which cetuximab was added to the simultaneous administration of CDDP and radiotherapy in treating local advanced head and neck cancer^[29]. According to their report, the three-year overall survival rate, the progression-free survival rate, and the local control rate were 76%, 56%, and 71% respectively, which were considered to be favorable.

4 Why is the response rate low with cetuximab mono-administration?

We focus on the fact that the evaluation of the mono administration of cetuximab in preclinical studies does not match that in clinical studies, even though the efficacy of the coadministration of cetuximab with chemotherapy and radiotherapy in preclinical studies almost matched those in clinical studies. In other words, we questioned why the response rate of cetuximab monoadministration to humans is low, at approximately 10%, despite the fact that the results of basic studies show that cetuximab has anti-tumor effects on head and neck squamous epithelial cell cancer. At present, the following two mechanisms are believed to be responsible for this.

A: The existence of cross-talk via PI3 Kinase/ Akt of EGFR and IGF1R

PI3K (phosphatidylinositol-1-3-OH kinase)/Akt survival signaling is known as an intracellular signaling route which is dependent on EGFR, and it is also downstream of IGF1R^[30-32]. Therefore, PI3K/ Akt signal activity is not inhibited, even if the phosphorylation of EGFR is inhibited by cetuximab. Thus, this suggests the possibility of co-administration of cetuximab and mTOR inhibitors to target PI3K/Akt signaling^[33].

B: The existence of crosstalk via STAT3 of EGFR and IL-6R

STAT3 is known as an intercellular signal which is dependent on EGFR^[34]. This is also a downstream signal of IL-6R^[35]. Therefore, the activity of STAT3 is not inhibited, even if cetuximab inhibits the phosphorylation of EGFR. Thus, this suggests the co-administration of cetuximab and STAT3-inhibitors^[36].

The above-mentioned two mechanisms are those of natural resistance to cetuximab treatment. The promotion of HB-EGF expression is also considered to be a mechanism of acquired resistance^[37].

5 Conclusion

The above suggests that the coadministration of cetuximab and drugs which inhibit Akt and STAT3 may significantly increase the monoadministration response rate of cetuximab [38]. Also, in clinical studies, the synergistic effect of coadministration of cetuximab has been limited to an increase in efficacy of 10-15% [39]. Further, the results of trials suggest that the addition of drugs which inhibit Akt and STAT3 may increase efficacy to that above currently-observed synergistic effects of the coadministration of cetuximab with existing chemotherapy or radiotherapy. In order to support this hypothesis, the different trials such as combination of cisplatin, cetuximab and temsirolimus in recurrent or metastatic squamous cell carcinoma of the Head and Neck (NCT01015664) are ongoing.

Since the beginning of the 21st century, multimodal therapy has been carried out for advanced head and neck cancers with poor prognosis, and prognoses have been gradually and slightly improving. We believe that studies which link basic research with the clinic will lead to the development of various molecular-targeted drugs, and the drastic improvement of prognoses going forwards.

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Conflict of interest

The author declares that there is no conflict of interest statement.

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